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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/616,409	ADAMS ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,25,139,142,144,166,210,251-260 and 338* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-18,24,25,30,81,90,97,139,142,144,166,168,177,182,184,188,191,195,197,210,251-261,290,320 and 338.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 18,24,30,81,90,97,168,177,182,184,188,191,195,197,261,290 and 320.

DETAILED ACTION

Election/Restrictions

The Election filed on August 2, 2005 in response to the Restriction Requirement of June 28, 2005 has been entered. Applicant's election of Group I, claims 1-17, 25, 139, 142, 144, 166, 210, 251-259 and 338, as specifically drawn to a method for stimulating an immune response in a subjet comprising administering to a subject in need of immune stimulation an agent of Formula I, and an antibody or antibody fragment, in an amount effective to stimulate an immune response, wherein the subject is suffering from cancer has been acknowledged.

Applicants election of Group I, claims 1-17, 25, 139, 142, 144, 166, 210, 251-259 and 338, with traverse is acknowledged. The traversal is on the grounds that the claim grouping of Group I. Specifically, Applicants requests the Examiner to reconsider rejoinder of claim 260 into Group I as its scope does not exclude subjects having cancer.

After careful review and reconsideration, Claim 260 will be examined along with Group I. However, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement pertaining to the other Groups, the Restriction Requirement is deemed proper and Final.

Claims 1-18, 24-25, 30, 81, 90, 97, 139, 142, 144, 166, 168, 177, 182, 184, 188, 191, 195, 197, 210, 251-261, 290, 320 and 338 are currently pending.

Claims 18, 24, 30, 81, 90, 97, 168, 177, 182, 184, 188, 191, 195, 197, 261, 290 and 320 are with drawn from consideration as being drawn to a non-elected invention.

Clams 1-17, 25, 139, 142, 144, 166, 210, 251-260 and 338 are under consideration.

Species Election

Applicants' election of the following species is acknowledged:

i) A species of antibody that is rituximab (Rituxan), and

ii) A species of cytokine that is IL-1.

After review and reconsideration, the Examiner has withdrawn the species elections.

Information Disclosure Statement

The Information Disclosure Statement filed on 05/02/2004 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

The information disclosure statement filed 06/27/2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17, 25, 139, 142, 144, 166, 210, 251-260 and 338 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-17, 25, 139, 142, 144, 166, 210, 251-260 and 338 are rejected as vague and indefinite for reciting the terms Formula I, Formula II, and Formula III as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify the agent of Formula I, II and III, for example, by chemical structure.

In addition, Claim 257 recites the limitation "wherein the IL-1 is IL-1a or IL-1b" in claim 1. However, a review of claim 1 does not appear to recite the limitation IL-1. As such, there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 8, 11, 14, 15, 25, 251, 253-254, 258, 260 and 338 are rejected under 35 U.S.C. 102(b) as being anticipated by Wallner et al. (WO 00/71135, 2000, IDS).

Wallner et al teach (abstract) a method of treating a subject with abnormal cell proliferation comprising administering to a subject an effective amount of an agent which appears to be 100% identical to the patentably disclosed agents of Formula's I and II as shown in the specification on page 25, wherein formula II is a cyclic derivative. With regards to the agent, the reference teaches (page 2, line 25 to page 3, line 17) that the agent is Val-boro-Pro, wherein the agent may be a racemic mixuture of the D/L isomers or may be the all L-isomer. Wallner et al. further teaches (page 43, lines 17+ and Figure 1) that IL-6 levels were increased upon the addition of the agent to Fischer D+ rat and BM stromal cells. Moreover, Wallner et al. disclose (page 22, lines 27-28 and page 25, line 23) that the method may further comprise administering the agent in combination with an anti-cancer agent such as a monoclonal antibody. With regards to the administration, the WO document teaches (page 27, lines 28-29 and page 28, lines 24-27) that the agents may be administered prior to, concurrent with, or following the monoclonal antibodies, wherein the monoclonal antibody may be administered at sub-lethal dose. Wallner et al. further teach (page 30, lines 6-10) that in subjects who require hemopoeitic stimulation and/or activation, the agents may be administered in different dosages or routes to achieve both hemopoeitic stimulation and proliferation at therapeutic levels. The reference further teaches that the agent may be administered to those patients who are free of symptoms calling for hematopoietic stimulation (page 3, lines 20-

23). In addition to those patients suffering from cancer, Wallner et al. teach that the subject may be HIV negative (page 3, line 27). Thus, while Wallner et al. does not characterize the immune response as antibody dependent cell-mediated cytotoxicty, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Ragnhammar et al. (Int. J. Cancer 1993; 53: 751-758), antibody-dependent cellular cytotoxicity (ADCC) is considered to be one the other effector functions of unconjugated monoclonal antibodies in tumor therapy. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure of administering a monoclonal antibody. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). Furthermore, although Wallner et al. does not explicitly teach that the agents stimulate the immune system, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Wallner et al. (WO 99/56753 1999, IDS), these agents can be used to boost the immune system (page 8, line 13). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure of administering a monoclonal antibody. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 12-13, 16-17, 139, 210 and 259 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallner et al. (WO 00/71135, 2000, IDS).

Wallner et al teach, as applied to claims 1-3, 8, 11, 14, 15, 25, 251, 253-254, 258, 260 and 338, a method of treating a subject with abnormal cell proliferation comprising administering to a subject an effective amount of an agent which appears to be 100% identical to the patentably disclosed agents of Formula's I and II (as shown in the specification on page 25) in combination with a

monoclonal antibody (page 22, lines 27-28 and page 25, line 23). With regards to the administration, the WO document teaches (page 27, lines 28-29 and page 28, lines 24-27) that the agents may be administered prior to, concurrent with, or following the monoclonal antibodies. Wallner et al. further teach (page 30, lines 6-10) that in subjects who require both hemopoeitic stimulation and/or activation and proliferation inhibition, the agents may be administered in different dosages or routes to achieve both hemopoeitic stimulation and proliferation at therapeutic levels.

Wallner et al. does not explicitly specify the timing in which the antibody is administered relative to the compound of Formula I.

However, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the administration times of the antibody and the compound of Formula I. One would have been motivated to do so because the selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results, see In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) or In re Gibson, 39 F.2d 975. Thus, one would have a reasonable expectation that the administration of the antibody simultaneously, sequentially or prior to the administration of the second therapeutic agent would result in the treatment of a tumor.

Claims 4, 9, 10, 142 and 144 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallner et al. (WO 00/71135, 2000, IDS) in further view of Hudziac et al. (5,725,856, 1998).

Wallner et al teach, as applied to claims 1-3, 8, 11-17, 25, 139, 210, 251, 253-254, 258-260 and 338, a method of treating a subject with abnormal cell proliferation comprising administering to a subject an effective amount of an agent which appears to be 100% identical to the patentably disclosed agents of Formula's I and II (as shown in the specification on page 25) in combination with a monoclonal antibody (page 22, lines 27-28 and page 25, line 23). With regards to the administration, the WO document teaches (page 27, lines 28-29 and page 28, lines 24-27) that the agents may be administered prior to, concurrent with, or following the monoclonal antibodies. Furthermore, the WO document teaches (page 31, lines 19-30) that the agent in combination with the monoclonal antibodies may be administered by various routes of administration such as oral and/or injection, wherein the particular route of administration depends on the agent selected, the

condition being treated, the severity of the condition, whether the treatment is therapeutic of prophylactic, and the dosage required for efficacy.

Wallner et al. does not explicitly teach that the antibody is administered via injection. Nor does Wallner et al. teach that the antibody is conjugated to a toxin or a chemotherapeutic agent.

Hudziac et al. teach a method of inhibiting growth of tumor cells comprising administering a monoclonal antibody directed towards the HER2 receptor (column 5, lines 8-19). With regards to administration, the patent teaches that the antibodies may be administered parentally to the target cell site (column 11, lines 36-37). Hudziac further teaches that in addition to administering the antibody alone, the antibodies may further be conjugated to a toxin (column 9, lines 55-67), small molecule anticancer drug (column 10, lines 2-3) or to a radioactive isotope (column 10, lines 24-27).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a monoclonal antibody to Her-2 alone or in combination with a cytotoxic moiety such as a toxin, radioactive isotope or chemotherapeutic agent in view of the teachings of Hudziac et al. One would have been motivated to do because as taught by Hudziac et al., monoclonal antibodies to Her-2 used either alone or in combination with a cytotoxic moiety may be used to treat a patient having a carcinoma (column 19 to 20, Claims). Thus, one of ordinary skill in the art would have reasonably expectation that by administering a compound of formula I or II in combination with the monoclonal antibodies as taught by Hudziac et al., one would achieve an effective method of treating tumors.

Further, it would have been prima facie obvious to one or ordinary skill in the art at the time the invention was made to optimize the routes of administration of antibody and the compound of Formula I, wherein the antibody is administered via injection and the agent of formula I is administered orally. One would have been motivated to do so because as taught by Hudziac et al., the preferred route of administration of the monoclonal antibody is via parental admnistration, while Wallner et al. teaches that the route of administration of the agent of Formula I includes oral administration but depends on a variety of conditions. The instant situation is amenable to the type of analysis set forth in In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) or In re Gibson, 39 F.2d 975 wherein the court held that performing process steps is *prima facie* obvious in the absence of new or unexpected results. Applying the same logic to the instant process claims, one of ordinary skill in the art would have reasonably expectation that by optimizing the routes of administration

relative to the agents used and/or condition, one would achieve an effective method of treating tumors.

Claims 4-7 and 166 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallner et al. (WO 00/71135, 2000, IDS) in further view of Borlsy et al. (2002/0165261 A1, 2001).

Wallner et al teach, as applied to claims 1-3, 8, 11-17, 25, 139, 210, 251, 253-254, 258-260 and 338, a method of treating a subject with abnormal cell proliferation comprising administering to a subject an effective amount of an agent which appears to be 100% identical to the patentably disclosed agents of Formula's I and II as shown in the specification on page 25. Moreover, Wallner et al. disclose (page 22, lines 27-28 and page 25, line 23) that the method may further comprise administering the agent in combination with an anti-cancer agent such as a monoclonal antibody.

Wallner et al. does not specifically teach that the antibody is the anti-HER2 antibody referred to as trastuzumab. Nor does Wallner et al. teach that the antibody is the anti-CD20 antibody referred to as rituximab.

Borsley et al. teach that chemotherapeutic drugs currently in use or in clinical trials include, but is not limited to rituximab and trastuzumab (page 1, paragraph 0006).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to treat cancer. One of skil in the art would have been motivated to do so because each of the therapeutics had been individually taught in the prior art to be successful at treating cancer. The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have reasonably expectation that by administering a compound of formula I or II in combination with the monoclonal antibodies as taught by Borsley et al., one would achieve an effective method of treating tumors.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established

scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Claim 252 and 255 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallner et al. (WO 00/71135, 2000, IDS) in further view of Wallner et al. (WO 99/56753 A1, 1999, IDS).

Wallner et al teach, as applied to claims 1-3, 8, 11-17, 25, 139, 210, 251, 253-254, 258-260 and 338, a method of treating a subject with abnormal cell proliferation comprising administering to a subject an effective amount of an agent which appears to be 100% identical to the patentably disclosed agents of Formula's I and II (as shown in the specification on page 25) in combination with a monoclonal antibody (page 22, lines 27-28 and page 25, line 23). Wallner et al. further teach (page 30, lines 6-10) that the agents may be administered in subjects who require hemopoeitic stimulation and/or activation.

Wallner et al. does not specifically teach that the agent of Formula I is an agent of Formula III. Nor does Wallner et al. teach that the agent of Formula I was administered in an effective amount to increase lymphoid tissue levels of IL-1.

Wallner et al. (1999) teach a method for hemopoeitic stimulation comprising administering an agent which appears to be 100% identical to the patentably disclosed agents represented as Formula's I-III. The WO document further teaches that the agents are administered in an amount to stimulate the production of growth factors, wherein the growth factor is IL-1.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute an agent as taught by Wallner et al. (1999) for the same purpose of hemopeotic stimulation as the agents taught by Wallner et al. (2000) . One of skill in the art would have been motivated to do so because each of the agents had been individually taught in the prior art to be successful at hemopeotic stimulation. Thus, one of ordinary skill in the art would have reasonably expectation that by substituting an agent taught by Wallner et al. (2000) for a compound as disclosed by Wallner et al. (1999), one would achieve a method for hemopeotic stimulation which can be applied to the treatment of tumors.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3 and 210 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 112 and 362 of copending Application No. 10/616,694.

Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. In the instant case, the method of stimulating an immune response in a subject comprising administering a compound of Formula I and an antibody claimed in the conflicting application appears to fall within the same scope of a method of stimulating an immune response in a subject comprising administering a compound of Formula I and an antibody claimed in the application being examined, and therefore, a patent to the method of stimulating an immune response, wherein the compound of Formula I is a genus, would necessarily extend the rights to a method of stimulating an immune response, wherein the compound of Formula I is a specific species, should the application being examined issue as a patent after the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
10/17/05